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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,162	01/13/2005	Kevin S. Brandt	FC-11-PUS	5437

26949 7590 07/16/2007

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
07/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,162	BRANDT, KEVIN S.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,6,12,14,15,19-24 and 26-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,6,12,14,15,19-24 and 26-31* is/are rejected.

7)☒ Claim(s) *12, 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 5/18/07 has been entered in full. Claims 1, 3, 5, 7-11, 13, 16-18 and 25 are canceled. Claims 4, 6, 15 and 21-24 are amended. New claims 26-31 are added.

Claims 2, 4, 6, 12, 14, 15, 19-24 and 26-31 are pending in the instant application.

Election/Restrictions

Applicant's election of Group II, claims 2, 4, 6, 12, 14, 15, 19-24 and 26-31, in the reply filed on 5/18/07 is acknowledged. Applicant does not indicate whether or not the restriction is with or without traverse, but because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that Applicants have cancelled all of the claims that were placed in Groups I, III and IV in the restriction requirement mailed 4/19/07.

Claims 2, 4, 6, 12, 14, 15, 19-24 and 26-31 are under consideration.

Specification

The disclosure is objected to because of the following informality:

The priority statement of the instant application's parent provisional and nonprovisional applications currently recites, "[t]his application claims priority to international PCT Application No. PCT/US03/21706, filed July 11, 2003". This statement should be amended to indicate that the instant application is a national-stage application filed under 35 U.S.C. § 371 of international PCT Application No. PCT/US03/21706 (as opposed to a continuation, divisional or continuation-in-part filed under 35 U.S.C. § 111(a) and claiming priority to said PCT application). It is noted that a notice of DO/EO Acceptance of the Application under 35 U.S.C. 371 and 37 CFR 1.495 (form PCT/DO/EO/903) was mailed 9/13/05.

Appropriate correction is required.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Applicant submitted an executed declaration on 5/18/07. However, this declaration is defective because non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the address of Applicant has been thrice altered without including a corresponding date. The execution of the declaration by said Applicant is not sufficient to meet this requirement. See MPEP 605.04(a): "Any changes made in ink in the application or oath prior to signing should be initialed and dated by the applicants prior to execution of the oath or declaration. The Office will not consider whether noninitialed and/or nondated alterations were made before or after signing of the oath or declaration but will require a new oath or declaration" [emphasis added].

Claim Objections

Claims 12 and 14 are objected to because of the following informalities:

Claims 12 and 14 are each objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Specifically, claims 12 and 14 each recite "[t]he nucleic acid molecule of Claims 2 and 4" instead of in an alternative (e.g., "the nucleic acid molecule of Claims 2 or 4"). For purposes of prosecution, claims 12 and 14 have been treated as if they recited the claims in the alternative form.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 6, 12, 14, 15, 19-24 and 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) an isolated nucleic acid that encodes a protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine, and the complement of said nucleic acid;

(2) an isolated protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine;

(3) a method to detect an inhibitor of octopamine receptor activity, said method comprising (a) contacting an isolated protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine, with a putative inhibitory compound in the presence of octopamine under conditions in which, in the absence of said compound, said protein has octopamine receptor activity and (b) determining if said putative inhibitory compound inhibits octopamine receptor protein activity;

(4) a method to produce a protein comprising culturing a cell transformed with a nucleic acid that encodes a protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine; and

(5) a recombinant molecule, virus, or isolated cell comprising a nucleic acid that encodes a protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine,

does not reasonably provide enablement for

(1) variants of an isolated nucleic acid that encodes a protein comprising the amino acid sequence of SEQ ID NO: 12, methods of use of said variants, or a recombinant molecule, virus or isolated cell comprising said variant;

(2) variants of an isolated protein comprising the amino acid sequence of SEQ ID NO: 12, or methods of use of said variants;

(3) a method to detect an inhibitor of octopamine receptor activity, said method comprising (a) contacting an isolated protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine, with a putative inhibitory compound in the absence of octopamine under conditions in which, in the absence of said compound, said protein has octopamine receptor activity and (b) determining if said putative inhibitory compound inhibits octopamine receptor protein activity; or

(4) a non-isolated cell comprising a nucleic acid encoding SEQ ID NO: 12.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is as follows. The specification teaches isolation of a nucleic acid named nCfOCR2136 (SEQ ID NO: 11 and its complement SEQ ID NO: 13; each 2136 nucleic acids) from the feline flea (*Ctenocephalides felis*). The specification teaches that SEQ ID NO: 11 encodes a predicted protein named PCfOCR712 (SEQ ID NO: 12; 712 amino acids). The specification states that SEQ ID NO: 11 "shared the most similarity, i.e., about 49% with a *D. melanogaster* [fruit fly] octopamine receptor nucleic acid molecule OAMB (GenBank accession number AF065443)" (pg 55, lines 14-20). In view of this similarity, the specification asserts that the protein of SEQ ID NO: 12 is an octopamine receptor of the feline flea. The specification does not provide any working examples wherein the protein of SEQ ID NO: 12 (or a variant) is shown to bind to octopamine, or demonstrate any "octopamine receptor protein activity". The specification does teach that the activity can be determined by the methods disclosed in

Han et al, 1996 (Neuron, 16: 1127-1135; cited as reference C6 on the 5/9/05 IDS). Applicant further discloses a series of fragments of SEQ ID NO: 11 or 12:

(1) an N-terminal protein fragment (SEQ ID NO: 7; 178 amino acids) encoded by a polynucleotide sequence (SEQ ID NO: 6; 868 nucleic acids); and the complement of said polynucleotide (SEQ ID NO: 8; 868 nucleic acids);
(2) a C-terminal protein fragment (SEQ ID NO: 4; 559 amino acids) encoded by a polynucleotide sequence (SEQ ID NO: 3; 2061 nucleic acids); and the complement of said polynucleotide (SEQ ID NO: 5; 2061 nucleic acids); and
(3) a nucleic acid fragment (SEQ ID NO: 1; 111 nucleic acids) and its complement (SEQ ID NO: 2; 111 nucleic acids).

The state of the prior art is as follows. The specification characterizes the prior art by stating, "[i]nsect octopamine receptor is a known target of various insecticides, including formamidine compounds such as demethylchlordimeform (DCDM)" and "in order to create compounds and treatments which are efficacious against fleas and/or ticks while minimizing toxicity to the host animal or non-target insect, it would be a distinct advantage to have the sequence of the flea and/or tick octopamine receptor" (pg 2, lines 9-17). The relevant prior art supports these statements made in the specification; specifically, Baxter et al (1999) teaches, "[m]ammals apparently lack a receptor for octopamine consequently, it is an excellent target for insecticides" (pg 462 of Baxter et al, 1999. Insect Biochemistry and Molecular Biology. 29: 461-467; cited as reference C2 on the 5/9/05 IDS). Baxter et al (1999) further teaches that, "little is known about interactions between octopamine and it receptor". The cloning of the OAMB gene is described in Han et al, 1998 (Journal of Neuroscience. 18(10): 3650-3658; cited as reference C5 on the 5/9/05 IDS). Han et al (1998) uses techniques previously disclosed in Han et al (1996; cited above) and referred to in the instant specification (see previous paragraph) to demonstrate OAMB protein activity. Specifically, Han et al (1998) teaches an increase in cyclic AMP (cAMP) and intracellular calcium $[Ca2+]_i$ levels in response to octopamine binding to the OAMB protein recombinantly expressed in host cells.

In view of the teachings of the specification and the prior art, the skilled artisan would predict that the protein of SEQ ID NO: 12 is an octopamine receptor that can bind

to octopamine, and would predict that said receptor would have activities in response to octopamine-binding that are similar to those taught by the prior art for the OAMB protein. However, the specification lacks enablement for the full breadth of the claims for the following reasons.

(1) The claims encompass a large genus of isolated nucleic acids encoding variants of SEQ ID NO: 12; isolated protein variants of SEQ ID NO: 12; methods of using said variants; and recombinant molecules, viruses and cells comprising said nucleic acids. For example, Claim 2 encompasses nucleic acids (and the complements thereof) that are at least 35 nucleotides in length and that hybridize to SEQ ID NO: 2, 5, 8 or 13 under specific conditions set forth in the claim, and which encode a protein that binds to octopamine. As described above, SEQ ID NO: 2, 5, 8 and 13 represent the complements of the sequences of SEQ ID NO: 1, 3, 6 and 11, and these complementary sequences would hybridize under the recited conditions. However, the sequences of SEQ ID NO: 1, 3 and 6 encode protein fragments of the protein of SEQ ID NO: 12. The protein encoded by SEQ ID NO: 1 is not disclosed in the specification but would consist of approximately 5% of the full-length protein (37 of 712 amino acids). SEQ ID NO: 3 encodes SEQ ID NO: 4, which is an N-terminal fragment consisting of approximately 78% of the full-length protein (559 of 712 amino acids). SEQ ID NO: 7 is a C-terminal fragment consisting of approximately 25% of the full-length protein (178 of 712 amino acids). The specification does not teach whether or not any of these fragments can bind to octopamine. Nor does the specification teach which specific residues in SEQ ID NO: 12 are required for octopamine binding. Furthermore, the claim is broadly directed to *any* nucleic acid of at least 35 nucleotides that can hybridize (under the recited conditions) with the complement of these fragments or the full-length sequence and that can bind octopamine. Fragments of SEQ NO: 11 of any length can hybridize with SEQ ID NO: 11. A nucleic acid sequence of 35 nucleotides encodes a protein of approximately 12 amino acids. Therefore, the claim encompasses a vast genus of nucleic acids encoding protein fragments of SEQ ID NO: 12 that range in size from the full-length protein to peptides are as small as 12 amino acids in length, and that can bind octopamine. However, the specification does not teach whether or not

each of these fragments can bind to octopamine. Nor does the specification teach any specific residues in SEQ ID NO: 12 that are required to octopamine binding. Finally, hybridization can occur between two nucleic acid sequences under stringent conditions even in the presence of one or more mismatches. This adds an additional level of complexity to the genus encompassed nucleic acid fragments, as each may have one or more nucleic acid changes that result in one or more amino acid changes in the encoded protein that may or may not alter octopamine binding.

Similarly, claim 4 encompasses any isolated nucleic acid molecule having a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 1, 3, 6 and 11, and that can bind to octopamine. SEQ ID NO: 11, the nucleic acid sequence encoding the full-length protein of SEQ ID NO: 12, consists of 2136 nucleotides. A nucleic acid that is 95% identical to SEQ ID NO: 11 can have up to 107 changes in the nucleic acid sequence (95% of 2136 is equivalent to 2029). This genus broadly includes those variants in which one nucleic acid is changed in 107 different codons of coding region. Therefore, this genus broadly includes a nucleic acid encoding a protein with as many as 107 different amino acids from the protein of SEQ ID NO: 12. As the protein of SEQ ID NO: 12 consists of 712 amino acids, this is equivalent to a protein with up to 15% of the protein changed (i.e., only 85% of the residues are identical to SEQ ID NO: 12). In addition, the genus broadly encompasses the aforementioned fragments (SEQ ID NO: 1, 3 and 6) each with up to 5% of the sequence changed. The specification does not disclose whether or not any of these variants can bind to octopamine.

Claim 6 encompasses proteins that are at least 95% identical to SEQ ID NO: 4, 7 or 12 and bind to octopamine. The full-length protein of SEQ ID NO: 12 consists of 712 amino acids. Therefore, the genus of protein variants with at least 95% identity to SEQ ID NO: 12 includes those with up to 35 amino acid changes anywhere in the protein sequence. Furthermore, the fragments SEQ ID NO: 4 (559 amino acids) and SEQ ID NO: 7 (178 amino acids) can have 28 and 9 changes, respectively, to the fragment sequence. However, because the claims encompass proteins "comprising" these fragments, the genus of encompassed proteins also includes those with any number of amino acid changes to the remainder of the protein. For example, a protein comprising

a sequence with 95% identity to SEQ ID NO: 7 can have up to 9 changes in the sequence of SEQ ID NO: 7 as well as an unlimited number of changes to the remainder of the protein (which is 534 amino acids).

Claims 12, 14, 19, 20 and 26-31 each encompass one or more of the isolated nucleic acid fragments and/or variants thereof described above, or isolated proteins encoded by said nucleic acids. Claim 12 limits the nucleic acid molecules to specific sequences, but this genus still includes those comprising SEQ ID NO: 1, 3 and 6 which encode fragments of the full-length protein. Claim 14 limits the nucleic acid molecules to those encoding a protein with a specific sequence, but this genus still includes those comprising SEQ ID NO: 4 or 7 which encode fragments of the full-length protein. Claim 19 limits the isolated protein to those with specific sequences, but this genus still includes those comprising protein fragments encoded by SEQ ID NO: 1, 3 or 6. Claim 20 limits the isolated proteins to those comprising specific sequences, but this genus still includes those comprising the fragments SEQ ID NO: 4 or 7. Claims 26-31 are in scope to claim 2, being directed to isolated nucleic acids that can hybridize to specific sequences, or to proteins encoded by said nucleic acids.

Claims 15, 21 and 22-24 are directed to methods of using said nucleic acids or proteins, or viruses or cells comprising said nucleic acids. Claim 15 is directed to a method of detecting an inhibitor of octopamine receptor activity, comprising contacting an isolated protein of claim 6 with a putative inhibitory compound and determining if the compound inhibits the receptor activity. Claim 21 encompasses a method of producing a protein encoded by a nucleic acid variant of the invention. Claims 22-24 respectively encompass a recombinant molecule (claim 22) or recombinant virus (claim 23), or recombinant cell comprising a nucleic acid variant of the invention.

While each of the claims described above requires that the encoded protein can bind to octopamine, the specification does not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of polypeptides of SEQ ID NO: 12. The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 12, nor sufficient guidance so as to enable one of skill in the art to make such a variant. As described above, Baxter et

al (1999) teaches that little is known about the interaction between octopamine and its receptor(s). The specification has failed to teach which amino acids of SEQ ID NO: 12 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 12 and yet still retain a characteristic of the parent polypeptide, e.g., the ability to bind octopamine. Applicant has not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 12 and variants of said protein.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a

starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and screen the same for octopamine-binding activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(2) With respect to claim 15, the claim encompasses a method to detect an inhibitor of octopamine receptor activity, said method comprising (a) contacting an isolated protein comprising the amino acid sequence of SEQ ID NO: 12, wherein said protein binds to octopamine, with a putative inhibitory compound under conditions in which, in which the absence of said compound, said protein has octopamine receptor activity and (b) determining if said putative inhibitory compound inhibits octopamine

receptor protein activity. The claim requires that the method be practiced "under conditions" in which the receptor has octopamine receptor activity. However, the specification does not provide any guidance as to conditions in which octopamine receptor activity can be produced without the presence of octopamine. In order to practice the claimed method without octopamine, the skilled artisan would first need to engage in experimentation to find other conditions which the protein of SEQ ID NO: 12 has "octopamine receptor activity". Such experimentation would be undue in view of the lack of guidance as to other ligands that would induce receptor activity and the need to screen large numbers of compounds in order to determine whether or not any other ligands even exist. Due to the large quantity of experimentation necessary to screen ligands for those that produce octopamine receptor activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art fails to teach another ligand for the receptor of SEQ ID NO: 12, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(3) With respect to claim 24, the claim encompasses cells comprising nucleic acids encoding variants of SEQ ID NO: 12 variants. These claims lack enablement for nucleic acids encoding variants of SEQ ID NO: 12 for the same reasons as described above. Furthermore, this claim is directed to a broad genus of cells exogenously expressing variants of SEQ ID NO: 12 (encoded by SEQ ID NO: 11). The specification contemplates two subgenera in which such host cells can be made and used. Specifically, the specification contemplates making and using the host cells in culture and in multicellular, transgenic organisms.

First, the specification contemplates making and using isolated host cells in culture to produce the encoded protein recombinantly. Such is enabled, since the specification and prior art provide specific guidance on how to make and use host cells for this purpose. Undue experimentation would not have been required of the skilled artisan to make and use the claimed host cells in this context.

Second, the specification clearly contemplates transgenic animals with cells exogenously expressing the polypeptides of the invention. The specification teaches (page 34, lines 11-18) that, "the present invention includes a recombinant cell comprising a host cell transformed with one or more recombinant molecules of the present invention. Transformation of a nucleic acid molecule into a cell can be accomplished by any method by which a nucleic acid molecule can be inserted into the cell. Transformation techniques include, but are not limited to, transfection, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. A recombinant cell may remain unicellular or may grow into a tissue, organ or a multicellular organism." The specification further contemplates that such transgenic multicellular organisms include fleas, ticks and host animals infested with either parasite (pg 42, lines 12-26).

However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the claimed gene "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183).

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that

establishes the unpredictability of making transgenic animals, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 2, 4, 6, 12, 14, 15, 19-24 and 26-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is claiming and what Applicant has possession of.

Claims 2, 4, 6, 12, 14, 15, 19-24 and 26-31 are genus claims because the claims are directed to variant isolated nucleic acid molecules, variant isolated proteins, methods of using said variant nucleic acid molecules and proteins, and recombinant molecules, viruses, and cells comprising said variant nucleic acids. Each genus is highly variant because a significant number of structural differences between genus members are permitted. The scope of each claimed genus is described above in the section titled, "Claim Rejections - 35 USC § 112, 1st paragraph, enablement".

From the specification, it is clear that Applicant has possession of an isolated nucleic acid molecule of SEQ ID NO: 11 that encodes a polypeptide of SEQ ID NO: 12. The specification fails to describe or teach any other polypeptide which differs from the sequence of SEQ ID NO: 12 and retains the characteristics of the parent polypeptide. The claims require that the encoded protein is functionally able to bind to octopamine. However, the instant specification fails to describe which protein residues can be altered in the sequence of SEQ ID NO: 12 and retain the ability to bind to octopamine.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics,

i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of encoded polypeptides related to SEQ ID NO: 12. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides,

and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule encoding a protein comprising SEQ ID NO: 12; an isolated protein comprising SEQ ID NO: 12; methods of using said nucleic acid molecules or proteins, and recombinant molecules, viruses, and cells comprising said variant nucleic acids, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Note

No nucleic acid or amino acid sequences were found in the prior art that are encompassed by the nucleic acid and amino acid sequences recited in the claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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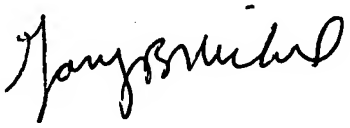

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